Ximatof™

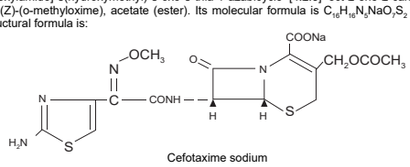
زیماٹوف

(Cefotaxime)

IV / IM Injection

Powder for Injection 250mg, 500mg & 1g

Ximatof (Cefotaxime) is a semisynthetic, broad spectrum cephalosporin antibiotic for parenteral administration. It is the sodium salt of 7-[2-(2-amino-4-thiazolyl) glyoxylamido]-3(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylate 72 (Z)-(o-methyloxime), acetate (ester). Its molecular formula is $C_{16}H_{16}N_5NaO_7S_2$ and the structural formula is:



Cefotaxime sodium

QUALITATIVE AND QUANTITATIVE COMPOSITION

Ximatof (Cefotaxime) is available for administration as:

Ximatof Powder for Injection 250mg
Each vial contains:
Cefotaxime sodium USP equivalent to Cefotaxime…250mg

Ximatof Powder for Injection 500mg
Each vial contains:
Cefotaxime sodium USP equivalent to Cefotaxime…500mg

Ximatof Powder for Injection 1g
Each vial contains:
Cefotaxime sodium USP equivalent to Cefotaxime…1g

CLINICAL PHARMACOLOGY

Mechanism of Action

Cefotaxime exerts its action by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thereby inhibiting cell wall synthesis.

Microbiology

Cefotaxime has been shown to be active against most isolates of the following bacteria both in vitro and in clinical infections.

Gram-positive bacteria
Enterococcus spp.[1]
Staphylococcus aureus (methicillin-susceptible isolates only)
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes (Group A beta-hemolytic streptococci)
Streptococcus spp. (Viridans group streptococci)

Gram-negative bacteria
Acinetobacter spp.
Citrobacter spp.[2]
Enterobacter spp.[2]
Escherichia coli [2]
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella spp. (including Klebsiella pneumoniae)[2]
Morganella morganii[2]
Neisseria gonorrhoeae (including beta-lactamase-positive and negative strains)
Neisseria meningitidis
Proteus mirabilis[2]
Proteus vulgaris[2]
Providencia rettgeri[2]
Providencia stuartii[2]
Serratia marcescens[2]

[1]*Enterococcus* species may be intrinsically resistant to Cefotaxime.
[2]Most extended spectrum beta-lactamase (ESBL)-producing and carbapenemase-producing isolates are resistant to Cefotaxime.

Anaerobic bacteria
Bacteroides spp., including some isolates of Bacteroides fragilis
Clostridium spp. (most isolates of Clostridium difficile are resistant)
Fusobacterium spp. (including Fusobacterium nucleatum)
Peptococcus spp.
Peptostreptococcus spp.

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following microorganisms exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to 1mcg/mL. However, the efficacy of Cefotaxime in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

Gram-negative bacteria
Providencia spp.
Salmonella spp. (including Salmonella typhi)
Shigella spp.

Pharmacokinetics

Absorption

Cefotaxime is for parenteral application. Mean peak concentrations 5 minutes after intravenous injection are about 81-102mg/l following a 1g dose of Cefotaxime and about 167-214mg/l 8 minutes after a 2g dose. Intramuscular injection produces mean peak plasma concentrations of 20mg/l within 30 minutes following a 1g dose.

Distribution

Cefotaxime gives good penetration into different compartments. Therapeutic drug levels exceeding the minimum inhibitory levels for common pathogens can rapidly be achieved. Cerebrospinal fluid concentrations are low when the meninges are not inflamed but Cefotaxime usually passes the blood-brain barrier in levels above the MIC of the sensitive pathogens when the meninges are inflamed (3-30µg/ml). Cefotaxime concentrations (0.2-5.4µg/ml), inhibitory for most gram-negative bacteria, are attained in purulent sputum, bronchial secretions and pleural fluid after doses of 1 or 2 g. High concentrations of Cefotaxime and O-desacetyl-cefotaxime are attained in bile. Cefotaxime passes the placenta and attains high concentrations in fetal fluid and tissues (up to 6mg/kg). Small amounts of Cefotaxime diffuse into the breast milk. Protein binding for Cefotaxime is approximately 25-40%. The apparent distribution volume for Cefotaxime is 21-37l after 1g intravenous infusion over 30 minutes.

Metabolism

Cefotaxime is partly metabolized in human beings. Approximately 15-25% of a parenteral dose are metabolized to the O-desacetyl-cefotaxime metabolite, which also has antibiotic properties.

Elimination

The main route of excretion of Cefotaxime and O-desacetyl-cefotaxime is the kidney. Only a small amount (2%) of Cefotaxime is excreted in the bile. In the urine collected within 6 hours 40-60% of the administered dose of Cefotaxime is recovered as unchanged Cefotaxime and 20% is found as O-desacetyl-cefotaxime. After administration of radioactive labelled Cefotaxime more than 80% can be recovered in the urine, 50-60% of this fraction is unchanged Cefotaxime and the rest contains metabolites. The total clearance of Cefotaxime is 240-390ml/min and the renal clearance is 130-150ml/min. The serum half-lives of Cefotaxime and O-desacetyl-cefotaxime are normally about 50-80 and 90 minutes respectively. In elderly, the serum half-life of Cefotaxime is 120-150min.

Special Population

Geriatrics

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Neonates

In neonates, the pharmacokinetics are influenced by gestation and chronological age, the half-life being prolonged in premature and low birth weight neonates of the same age.

Renal Impairment

In severe renal dysfunction the elimination half-life of Cefotaxime itself is increased minimally to about 2.5 hours, whereas that of desacetyl-cefotaxime is increased to about 10 hours. Total urinary recovery of Cefotaxime and its principal metabolite decreases with reduction in renal function.

THERAPEUTIC INDICATIONS

Ximatof (Cefotaxime) is indicated for the treatment of the following infections due to susceptible microorganisms:
- Respiratory tract infections.
- Genitourinary infections.
- Gynecologic infections.
- Bacteremia/Septicemia.
- Skin and skin structure infections.
- Intra-abdominal infections.
- Lyme-borreliosis (especially stages II and III).
- Bone and/or joint infections.
- Central nervous system infections.
- Endocarditis.

Peri-operative prophylaxis in surgical procedures such as colorectal, gastrointestinal, prostatic, urogenital and gynecological surgery in patients who have a definite risk of post-operative infections. Cefotaxime should be used in combination with another antibiotic that can provide anaerobic cover in the treatment of intra-abdominal infections. Cefotaxime should be used in combination with an aminoglycoside in the treatment of infections caused by Pseudomonas.

Method of Administration

Specimens for bacteriologic culture should be obtained prior to therapy in order to isolate and identify causative organisms and to determine their susceptibilities to Cefotaxime. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

DOSAGE AND ADMINISTRATION

Adults

Ximatof (Cefotaxime) may be administered by intravenous bolus injection, by intravenous infusion, or by intramuscular injection, Dosage and route of administration should be determined by susceptibility of the causative organisms, severity of the infection, and the condition of the patient (see table for dosage guideline). The maximum daily dosage should not exceed 12g.

Guidelines for dosage of Ximatof

Type of infection	Daily dose (grams)	Frequency and route
Gonococcal urethritis / cervicitis in males and females	0.5	0.5g IM (single dose)
Rectal gonorrhea in females	0.5	0.5g IM (single dose)
Rectal gonorrhea in males	1	1g IM (single dose)
Uncomplicated infections	2	1g every 12 hours IM or IV
Moderate to severe infections	3-6	1-2g every 8 hours IM or IV
Infections commonly needing antibiotics in higher dosage (e.g., septicemia)	6-8	2g every 6-8 hours IV
Life-threatening infections	Up to 12	2g every 4 hours IV

If *C. trachomatis* is a suspected pathogen, appropriate anti-chlamydial coverage should be added, because Cefotaxime sodium has no activity against this organism.
To prevent postoperative infection in contaminated or potentially contaminated surgery, the recommended dose is a single 1g IM or IV administered 30 to 90 minutes prior to start of surgery.

Lyme borreliosis

A daily dose of 6g Cefotaxime (14 to 21 days duration). The daily dose was generally administered divided into 3 parts (2g Cefotaxime 3 times daily).

Cesarean Section Patients

The first dose of 1g is administered intravenously as soon as the umbilical cord is clamped. The second and third doses should be given as 1g intravenously or intramuscularly at 6 and 12 hours after the first dose.

Neonates, Infants, and Children

The following dosage schedule is recommended:

Neonate (birth to 1 month)
0-1 week of age 50mg/kg per dose every 12 hours IV
1-4 weeks of age 50mg/kg per dose every 8 hours IV
It is not necessary to differentiate between premature and normal-gestational age infants.

Infants and Children (1 month to 12 years)
For body weights less than 50kg, the recommended daily dose is 50 to 180mg/kg IM or IV body weight divided into four to six equal doses. The higher dosages should be used for more severe or serious infections, including meningitis. For body weights 50kg or more, the usual adult dosage should be used; the maximum daily dosage should not exceed 12g.

Perioperative Prophylaxis

For perioperative infection prophylaxis the administration of a single dose of 1 to 2g Cefotaxime 30 to 60 minutes prior to the operation is recommended. Another antibiotic to cover anaerobic organisms is necessary. A repeat dose is required if the duration of the operation exceeds 90 minutes.

Renal Impaired Patients

With patients with a creatinine clearance of 20ml/minute or less, the maintenance dose is reduced to half the normal dose. With patients with a creatinine clearance of 5ml/minute or less, a reduction of the maintenance dose to 1g Cefotaxime (divided into 2 individual administrations at 12 hour intervals), seems to be appropriate. The stated recommendations are based on experiences with adults.
Since Cefotaxime is to a large extent eliminated by hemodialysis, an additional dose should be administered to patients who are dialyzed, after the dialysis procedure.

NOTE: As with antibiotic therapy in general, administration of Cefotaxime Sodium should be continued for a minimum of 48 to 72 hours after the patient defervesce or after evidence of bacterial eradication has been obtained; a minimum of 10 days of treatment is recommended for infections caused by Group A beta-hemolytic streptococci in order to guard against the risk of rheumatic fever or glomerulonephritis; frequent bacteriologic and clinical appraisal is necessary during therapy of chronic urinary tract infection and may be required for several months after therapy has been completed; persistent infections may require treatment of several weeks and doses smaller than those indicated above should not be used.

Preparation of Ximatof (Cefotaxime) Injection

As a general rule the solution should be used immediately after preparation.
Ximatof (Cefotaxime) for IM or IV administration should be reconstituted as follows:

Strength	Diluent (mL)
250mg vial	2mL
500mg vial	2mL
1g vial	4mL

Solutions of Ximatof (Cefotaxime) range from very pale yellow to light amber, depending on concentration, diluent used, and length and condition of storage.

For intramuscular use
Reconstitute Ximatof (Cefotaxime) vials with Sterile Water for Injection as described above.

For intravenous use
Reconstitute Ximatof (Cefotaxime) vials with Sterile Water for Injection as described above. For IV Infusion, the following solutions may be used: Sterile Water for Injection, Sodium Chloride 0.9%, Dextrose 5% and 10%, Ringer's Solution and Ringer-Lactate Solution.

NOTE: Solutions of Ximatof (Cefotaxime) must not be admixed with aminoglycoside solutions. If Ximatof (Cefotaxime) and aminoglycosides are to be administered to the same patient, they must be administered separately and not as mixed injection.

IM Administration
As with all IM preparations, Ximatof (Cefotaxime) should be injected well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel.

Individual IM doses of 2g may be given if the dose is divided and is administered in different intramuscular sites.

IV Administration
For intermittent IV administration, the solution can be injected over a period of three to five minutes. Cefotaxime should not be administered over a period of less than three minutes. With an infusion system, it may also be given over a longer period (50 – 60 minutes) of time through the tubing system by which the patient may be receiving other IV solutions. However, during infusion of the solution containing Ximatof (Cefotaxime), it is advisable to discontinue temporarily the administration of other solutions at the same site.

After reconstitution, solution for injection can be stored at 25°C for up to 12 hours or in the refrigerator (2°C - 8°C) for up to 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

ADVERSE REACTIONS
Very Common
Pain at the injection site.

Uncommon
Leucopoenia, eosinophilia, thrombocytopenia, jarisch-herxheimer reaction, convulsions, diarrhea, increase in liver enzymes (ALAT, ASAT, LDH, gamma GT and or alkaline phosphatase) and/or bilirubin, rash, pruritls, urticarial, decrease in renal function/increase of creatinine (particularly when co-prescribed with aminoglycosides), fever, inflammatory reactions at the injection site including phlebitis, thrombophlebitis.

Not known
Superinfection, neutropenia, agranulocytosis, hemolytic anemia, anaphylactic reactions, angioedema, bronchospasm, anaphylactic shock, headache, dizziness, encephalopathy (e.g. impairment of consciousness, abnormal movements, arrhythmia following rapid bolus infusion through central venous catheter, nausea, vomiting, abdominal pain, pseudomembranous colitis, hepatitis (sometimes with jaundice), erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, Interstitial nephritis, systemic reactions to lidocaine (if reconstituted with lidocaine).

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
Cefotaxime is contraindicated in patients who have shown hypersensitivity to Cefotaxime sodium, or the cephalosporin group of antibiotics or previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other type of beta-lactam drug.

PRECAUTIONS
General
As with other antibiotics, the use of Cefotaxime, especially if prolonged, may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during treatment, appropriate measures should be taken.

Prescribing Cefotaxime in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Because high and prolonged serum antibiotic concentrations can occur from usual doses in patients with transient or persistent reduction of urinary output because of renal insufficiency, the total daily dosage should be reduced when Cefotaxime is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organism.

Cefotaxime, like other parenteral anti-infective drugs, may be locally irritating to tissues. In most cases, perivascular extravasation of Cefotaxime responds to changing of the infusion site. In rare instances, extensive perivascular extravasation of Cefotaxime may result in tissue damage and require surgical treatment. To minimize the potential for tissue inflammation, infusion sites should be monitored regularly and changed when appropriate.

Anaphylactic reactions
Cefotaxime should be used with caution in persons with a history of allergies or asthma. If a hypersensitivity reaction occurs, treatment must be stopped.

Serious bullous reactions
Cases of serious bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with Cefotaxime. Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Clostridium difficile associated disease (e.g. pseudomembranous colitis)
Diarrhea, particularly if severe and/or persistent, occurring during treatment or in the initial weeks following treatment, may be symptomatic of Clostridium difficile associated disease (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis.
If a diagnosis of pseudomembranous colitis is suspected, Cefotaxime should be stopped immediately and appropriate specific antibiotic therapy should be started without delay.

Hematological reactions
Leucopenia, neutropenia and more rarely, agranulocytosis, may develop during treatment with Cefotaxime, particularly if given over long periods. For treatment courses lasting longer than 7-10 days, the blood white cell count should be monitored and treatment stopped in the event of neutropenia.
Some case of eosinophilia and thrombocytopenia, rapidly reversible on stopping treatment, have been reported. Cases of hemolytic anemia have also been reported.

Patients with renal insufficiency
The dosage should be modified according to the creatinine clearance calculated. Caution should be exercised if Cefotaxime is administered together with aminoglycosides or other nephrotoxic drugs. Renal function must be monitored in these patients, the elderly and those with pre-existing renal impairment.

Neurotoxicity
High doses of beta lactam antibiotics including Cefotaxime, particularly in patients with renal insufficiency, may result in encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions). Patients should be advised to contact their doctor immediately prior to continuing treatment if such reactions occur.

Precautions for administration
Potentially life-threatening arrhythmia has been reported in a very few patients who received rapid intravenous administration of Cefotaxime through a central venous catheter. The recommended time for injection or infusion should be followed.

Effects on Laboratory Tests
As with other cephalosporins, a positive Coombs test has been found in some patients treated with Cefotaxime. This phenomenon can interfere with the cross-matching of blood.

In glucose determinations in urine and blood, false positive as well as false negative results may also be obtained, depending on the method; these may be avoided by the use of enzymatic methods.

Pregnancy
There are, no adequate and well controlled studies in pregnant women. Therefore, Cefotaxime should not be used during pregnancy unless the anticipated benefit outweighs any potential risks.

Nursing Mothers
Cefotaxime is excreted into human breast milk. Therefore, a decision must be made whether to discontinue breast-feeding or to discontinue therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

DRUG INTERACTIONS
Cefotaxime / Other Antibiotics
- As far as possible, Cefotaxime should not be combined with substances having a bacteriostatic action (e.g. tetracycline, erythromycin, chloramphenicol or sulfonamides), since antagonistic effect has been observed regarding the anti-bacterial effect in vitro. A synergistic effect can result with the combination with aminoglycosides.
- An increased risk of ototoxicity and nephrotoxicity has been reported when Cefotaxime has been used concomitantly with cephalosporins or aminoglycosides. Dose adjustment may be necessary, and the kidney function must be watched.

Cefotaxime / Probenecid
The simultaneous administration of Probenecid leads to higher, more prolonged plasma concentrations of Cefotaxime by interfering with renal tubular transfer thereby delaying excretion.

Cefotaxime / Potentially Nephrotoxic Drugs and Loop Diuretics
In combination with potentially nephrotoxic drugs (such as, for example, aminoglycoside antibiotics, NSAIDs, polymyxin B and colistin) and with potent diuretics, (e.g. furosemide) the kidney function should be monitored, since the nephrotoxicity of the substances quoted may be accentuated.

OVERDOSAGE
Symptoms of overdose may largely correspond to the profile of side effects. There is a risk of reversible encephalopathy in cases of administration of high doses of β-lactam antibiotics including Cefotaxime.
In case of overdose, Cefotaxime must be discontinued, and supportive treatment initiated, which includes measures to accelerate elimination, and symptomatic treatment of adverse reactions (e.g. convulsions).
No specific antidote exists. Serum levels of Cefotaxime can be reduced by hemodialysis or peritoneal dialysis.

STORAGE
Do not store above 30°C.
Protect from light & moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Ximatof (Cefotaxime) Powder for Injection 250mg is available in unit pack size of 1 vial along with a 2mL ampoule of Sterile Water for Injection.

Ximatof (Cefotaxime) Powder for Injection 500mg is available in unit pack size of 1 vial along with a 2mL ampoule of Sterile Water for Injection.

Ximatof (Cefotaxime) Powder for Injection 1g is available in unit pack size of 1 vial along with a 4mL ampoule of Sterile Water for Injection.

Keep out of reach of children.

To be sold on a prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
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